Sex Steroid Hormones, Bone Mineral Density, and Risk of Breast Cancer

Lewis H. Kuller,[1] Jane A. Cauley,[1] Lee Lucas,[1] Steve Cummings,[2] and Warren S. Browner[3]

[1]University of Pittsburgh, Department of Epidemiology, Pittsburgh, Pennsylvania; [2]University of California, San Francisco, California; [3]VA Medical Center, San Francisco, California

Increased bone mineral density (BMD), as a marker of higher integrated estrogen exposure over time, could be an important risk factor for postmenopausal breast cancer. In the Study of Osteoporotic Fractures 8065 non-black women age 65 years and older were followed for an average of 3.2 years. There were 121 incident breast cancer cases. The age adjusted incidence rate/1000 person years of breast cancer was substantially higher among women with high BMD at several measured bone sites. There was approximately a 2-fold higher risk of breast cancer for women in the upper as compared to the lower 25th percentile of BMD. Considerable controversy exists about the association of hormone replacement therapy (HRT) and increased risk of breast cancer. In this paper we modeled the effects of selection for HRT, presuming that women with lower BMD would be more likely to be on HRT, then estimated the observed versus potential risk of breast cancer among HRT users as compared to nonusers. The model suggests that the potential risk of breast cancer associated with HRT could be greatly underestimated and that postmenopausal women with high BMD who are placed on HRT could have a substantially increased risk of breast cancer. This model of increased risk of breast cancer associated with BMD and HRT needs to be evaluated within clinical trials and larger observational studies that include measures of BMD. — *Environ Health Perspect* 105(Suppl 3):593–599 (1997)

Key words: bone mineral density, estrogen, hormone replacement therapy, breast cancer

Introduction

The use of exogenous estrogen and progesterone therapy among postmenopausal women and the subsequent risk of breast cancer remains a very controversial subject. There is little consistency in relative risks (RR) of hormone replacement therapy (HRT) and breast cancer across many studies (*1*). The widespread and increasing use of HRT could be of major concern if such therapy was actually associated with an increased risk of breast cancer. There are several factors that could account for inconsistent study results on the relationship between exogenous hormone therapy and risk of breast cancer. The first and most important is probably selection bias among postmenopausal women given HRT. Women at lower risk for breast cancer are more likely to be placed on HRT (*2*).

Second, the duration of follow-up for women on HRT has not been long enough to identify either a morbidity (i.e., an increase in incidence) or increased mortality from breast cancer (*3*). A third hypothesis is that estrogen or estrogen/progesterone therapy is not an important determinant of the risk of breast cancer (*4*).

In this paper we will briefly review the model for the development of breast cancer among postmenopausal women. Using data from the Study of Osteoporotic Fracture (SOF) we measured the relationship between bone mineral density (BMD) and risk of breast cancer. We then modeled the potential risk of breast cancer for women on HRT based on BMD as a selection criteria. We also investigated whether changes in the selection criteria for HRT use (that is, placing women who have high BMD, high body weight, or high lipid levels on HRT) could increase the estimated risk for breast cancer.

A plausible hypothesis linking host susceptibility, environmental agents, and hormones to the risk of breast cancer is as follows: *a*) The early neoplastic changes of breast cancer are caused by exposure to a variety of chemical carcinogens that are secreted by breast glandular tissue. The exposure is more important at an earlier age (*5,6*). Susceptibility of breast tissue to specific agents is clearly age dependent, as suggested by the substantially reduced risk of breast cancer at first full-term pregnancy. This is probably due to differentiation of breast glandular tissue, and differences in the risks of breast cancer related to age with exposure to radiation (a causal agent for breast cancer) (*7*). *b*) The growth of breast neoplasms to clinical disease is primarily determined by sex steroid hormone levels, especially estrogens, and estogen metabolism (*5,8,9*). *c*) The progression to metastatic disease may be related to a secondary exposure to carcinogens in cells with higher mitotic activity secondary to hormone stimulation later in life (*5*). *d*) Genetic host susceptibility plays an important role, possibly related to the metabolism of the carcinogens, such as P450 polymorphisms (*10,11*), genetic polymorphisms that affect sex steroid hormone metabolism or receptors (*12*), or mutations in oncogenes or suppressor genes such as *p53*—as yet unknown effects related to BRCA (*13*).

Endogenous Estrogen and Breast Cancer

The levels of endogenous estrogen exposure at the breast and the specific metabolites of estrogen (*14*) play key roles in determining whether early neoplastic changes in the breast progress to clinical breast cancer and metastatic disease. Breast cancer may be prevented by modulating the levels and metabolism of estrogens, either by drugs or by lifestyle modification. Similar increased estrogen exposure at the breast, either due to lifestyle risk factors, genetic factors, or exogenous hormone therapy, i.e., HRT could result in an increased incidence of breast cancer (*14*).

This paper was presented in part at the Workshop on Hormones, Hormone Metabolism, Environment, and Breast Cancer held 28–29 September 1995 in New Orleans, Louisiana. Manuscript received at *EHP* 6 June 1996; manuscript accepted 8 October 1996.

This work was supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases grant 5 R01 AR35582-09 and Cancer Center Support grant CA47904.

Address correspondence to Dr. L.H. Kuller, University of Pittsburgh, GSPH Department of Epidemiology, 130 DeSoto Street, Pittsburgh, PA 15261. Telephone: (412) 624-3054. Fax (412) 624-7397. E-mail: kuller+@pitt.edu

Abbreviations used: BMD, bone mineral density; BMI, body mass index; BRCA, breast cancer associated; HDLc, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; IGF, insulinlike growth factor; LDLc, low-density lipoprotein cholesterol; PEPI, Perimenopausal Estrogen/Progesterone Intervention; RR, relative risk; SOF, Study of Osteoporotic Fractures.

The level of estrogens and progesterone are much higher among pre- as compared to postmenopausal women (*15,16*). The variability of blood estrogen levels during the menstrual cycle has made it extremely difficult to evaluate the relationship between premenopausal blood estrogen levels and the risk of breast cancer (*16,17*). It is unclear whether peak estogen levels during the menstrual cycle, average estrogen levels over the cycle, or perhaps, levels during the luteal or follicular phases are important risk factors for breast cancer.

The importance of endogenous estrogen levels and risk of premenopausal breast cancer are primarily documented by the substantial reduction in risk associated with oophorectomy (*18*) (especially at an early age), and the benefits of oophorectomy (*19*) and tamoxifen (*20*) in improving survival among premenopausal breast cancer patients. Genetic factors (i.e., host susceptibility) play a very important role in premenopausal breast cancer. The levels of endogenous estrogens necessary to stimulate growth of breast cancer cells may be lower than found in most women during a normal menstrual cycle. An effect of BRCA protein may be to reduce the risk of breast neoplasia by decreasing the active mitotic activity due to increased exposure to estrogens or estrogen/progesterone during menstrual cycles.

Postmenopausal estrogens are much lower than premenopausal levels and are primarily produced by the aromatization of androstenedione in fat tissue (*21*). The primary estrogen in postmenopausal women is estrone, which is not bound to sex hormone-binding globulin. A small amount of testosterone is also produced for a period of time by the postmenopausal ovary (*22*). The level of postmenopausal estrogens may, therefore, be related to the production of androstenedione in the adrenal gland and the aromatization of androstenedione to estrone, primarily in fat tissue.

Studies of the relationship between blood estradiol and estrone levels among postmenopausal women and the risk of breast cancer have had major limitations. The blood levels of postmenopausal estrogens are very low. Without careful attention to measurement techniques, cross reactivity, lack of accuracy, and variability of the assay may result in reported spurious levels of estradiol (*23*).

The levels of estrone and estradiol early in the postmenopause (first several years after the menopause) are related to residual ovarian secretion of estrogens, as well as the aromatization of androstenedione (*15,16,24*). Estradiol levels early in the postmenopause correlate poorly with levels later in menopause and there is no apparent relationship between estrogen levels in premenopause and levels in the same women in postmenopause (*24*). Postmenopausal estradiol levels are not related to premenopausal level nor to the levels early in the postmenopause.

Estradiol is weakly bound to sex hormone-binding globulin and recent interest has focused on whether the free estradiol levels may be a better measure of risk of breast cancer. Free levels of estradiol are extremely difficult to measure accurately among postmenopausal women. Levels of sex hormone-binding globulin may be used to estimate the percentage of free estradiol (*25*).

Endogenous Estrogens and Other Biological Associations

The measurement of postmenopausal estrogen levels do appear to have other biological associations in addition to possible risk of postmenopausal breast cancer. Women who report hot flashes during the perimenopause and early in the postmenopause have lower blood estradiol levels (*26*). A positive association has been noted between blood estradiol and estrone levels and BMD among postmenopausal women that appears to be independent of obesity (*27*). There is a suggestive association of higher estradiol and lower low-density lipoprotein cholesterol (LDLc) levels among postmenopausal women (*28*).

There have been both case–control and longitudinal studies of the association of endogenous estrogen levels and risk of breast cancer (*1,4,5*). The results of these studies are inconsistent. More recent prospective studies have documented an increased risk of breast cancer with higher levels of postmenopausal blood estrogens, especially free or non-sex hormone-bound estradiol levels (*29*).

However, all of the associations between blood estrone and estradiol levels and biological measurements (breast, bone, hypertrophy, lipids) are relatively weak, due to the variability of the measurements of estrone and estradiol. The blood levels are a measure of production, secretion, and metabolism of estrogens (*16*). Estrogen levels at specific tissue such as the breast may not necessarily be measured by blood levels (*30*). Fat tissue in the breast can aromatize androstenedione to estrone and then to estradiol. Sulfatases, also in the breast, can convert estrone sulfate to estrone. Therefore, exposure of the postmenopausal breast to estrogens is certainly higher and may be quite different from levels reported in the blood (*5,31*). It is extremely difficult to measure estrogen levels in breast tissue in epidemiological studies among postmenopausal women, especially in prospective studies where large numbers of healthy women must be followed over a long period of time.

Determinants of Endogenous Estrogens

The primary determinants of postmenopausal estrone and estradiol levels are obesity or body fat. In the Healthy Women Study we showed that postmenopausal levels (5–8 years postmenopausal) of both estrone and estradiol were directly related to body mass index (BMI) (*28*). The strong association between BMI and postmenopausal estrone and estradiol levels has been documented in many epidemiological studies (*5*). Several studies show an association between obesity among postmenopausal women and risk of breast cancer (*5*).

Obesity and body fat distribution are major determinants of sex hormone-binding globulin. The sex hormone-binding globulin levels decrease substantially with increasing levels of obesity among postmenopausal women (*32*). The degree of obesity (*33*), the amount of intraabdominal fat, and the waist-to-hip ratio (*34*) have all been related to the increased risk of breast cancer. The levels of sex hormone-binding globulin and any relationship to breast cancer may, therefore, be only a measure of the degree of obesity and the high correlation with levels of sex hormone-binding globulin.

Estradiol is also more weakly bound to sex hormone-binding globulin than testosterone (*32*). The levels of sex hormone-binding globulin may be a measure of the relative amount of free testosterone to free estradiol. This ratio (estradiol/testosterone) could be related to risk of breast cancer. Recent studies have shown that higher free testosterone levels in postmenopausal women are risk factors for breast cancer (*35*).

Bone Mineral Density and Endogenous Estrogens

BMD could be a significant pre- and postmenopausal marker for long-term estrogen exposure. Therefore, measurement of BMD, even in older women, could be a significant measure of lifetime

estrogen exposure. Clearly, diet, genetic attributes, and other growth factors affect BMD. Estrogens, however, play a crucial role in BMD in women. If higher lifetime exposure to endogenous estrogens is associated with higher BMD, then we hypothesize that women with higher BMD should have an increased risk of breast cancer (*36*).

Bone contains estrogen receptors and is highly sensitive to estrogen levels (*37*). Early age at menarche, length of reproductive life, and normal cycling are associated with higher BMD (*38*).

The peri- to postmenopause is associated with substantial bone loss due to the decrease in estrogen production by the ovary (*39*). As noted, we have found that endogenous estrogen levels are independently related to BMD among older women (*27*). Estrogen drug therapy and resulting higher blood estrogen levels are also associated with a decrease in the rate of bone loss and fractures among older women (*40*). Greater degrees of obesity and higher estrogen levels correlate with higher BMD, even for nonweight-bearing sites (*27*).

Methods

The SOF recruited 9704 women aged 65 years and older in four locations in the United States: Baltimore, Maryland; Minneapolis, Minnesota; Monongahela Valley, Pennsylvania; and Portland, Oregon (*41,42*). All women studied were white. Approximately 1 year after their baseline examination, participants completed a questionnaire that included personal history of breast cancer. Further follow-up to determine incidence of breast cancer was completed approximately 3.2 years after this questionnaire (1.0–6.6 years on average).

Breast cancer analysis was limited to women who provided information regarding their breast cancer status both at the year 1 exam and approximately 3.2 years later. Women who reported breast cancer at year 1 were considered to be prevalent cases and excluded from the analysis (n=506). Three hundred sixty-five women died before complete follow-up information on breast cancer was available. For 30 of the women, breast cancer was the underlying cause of death. Of those 30 deaths, 22 were prevalent cases (women had reported a history of breast cancer at the year 1 exam). Three were considered possible incident cases; five were missing information about breast cancer history. The study included 121 breast cancer cases. Medical records for all breast cancer cases were reviewed to validate the diagnosis. Four of the 121 breast cancer cases were considered carcinoma *in situ* (*41*).

BMD was measured at entry to the study using an Osteo analyzer (Siemens Osteon, Wahiwa, HI). The distal and midradius and the calcaneus were scanned at the baseline examination. During a second clinical examination (approximately 2 years after baseline), measurements of BMD at the proximal femur and lumbar spine (L1–4) using Dual Energy X-ray Absorptiometry (DEXA) 1000 (Hologic, Waltham, MA) were added (*42*). Both measurements are associated with relatively small coefficients of variation of the measurements (1.5% distal radius, 2.0% midradius, 1.3% calcaneous, 1.2% femoral neck and 1.5% lumbar spine) (*42*).

The study included information about weight, height, self-reported height at age 25 years, reproductive history, family history of breast cancer, and history of benign breast disease. Blood samples were also obtained and are currently being analyzed for sex-steroid hormone levels (*41*).

Results

The age-specific incidence rates (95% CI) of breast cancer (per 1000 person years) were (n=56) 4.59 (3.53–5.97) age 65 to 69 years; (n=41) 4.85 (3.57–6.60) age 70 to 74 years; (n=25) 3.94 (2.66–5.83) age 75 years and older. The incidence rates are comparable to those reported for the SEER study (*43*).

The incidence of breast cancer increased with the level of BMD at all measured anatomical sites. For example, at the proximal radius the incidence (95% CI) was 2.5 (1.46–4.35) in the lowest quartile of BMD and 4.06 (2.06–6.23) in the second quartile, 5.10 (3.50–7.43) in the third quartile, and 5.48 (3.86–7.79) in the fourth quartile per 1000 person years. Adjustment for age and other breast cancer risk factors did not affect the association of BMD with risk of breast cancer. Current estrogen therapy use was reported in a greater proportion of breast cancer cases (20%) than controls (14%) (p=0.10). The RR associated with current estrogen use (1.45) is consistent with several other studies of long-term estrogen use. Current estrogen users had higher BMD than nonusers. Restriction of the analysis, however, to women who were not current estrogen users had no effect on the association between BMD and risk of breast cancer. Thus, women with high BMD (upper quartile) at any one of five sites had approximately 2.5- to 3-fold greater risk of incident breast cancer.

The measurements of BMD at the three sites (distal and proximal radius and calcaneus) are not perfectly correlated. Therefore, we further tested the hypothesis to determine if women who have low BMD at all three sites (proximal and distal radius and the oscalsis) (i.e., presumably women with the lowest long-term estrogen exposure) would be at very low risk of breast cancer. At all three sites, 793 controls and only three cases were in the lowest quartile of BMD. The RR of breast cancer was greatly reduced for women with low BMD at all three sites [0.23 (0.07–.72) (Figure 1)] compared with women who were in the top quartile of BMD for at least one site, although the number of cases was relatively small and confidence intervals fairly wide.

Preliminary results from the SOF recently reported by Cummings et al. (*44*), further support the association of low risk of breast cancer with possible osteoporosis or low BMD. Vertebral fractures were ascertained in the SOF at baseline by X-ray and morphometric analysis. Women with vertebral fractures at baseline had 62% lower risk of subsequent breast cancer over the 3.2 years of follow-up [RR 0.4 (0.2–0.08)] than women without vertebral fractures. Even adjustment for BMD had little effect on the strong reduction in risk of breast cancer associated with vertebral fracture, as diagnosed by X-ray.

Model: Bone Mineral Density, Exogenous Estrogen, and Breast Cancer

We modeled the results of the SOF (the study of the relationship between BMD and risk of breast cancer) in order to further

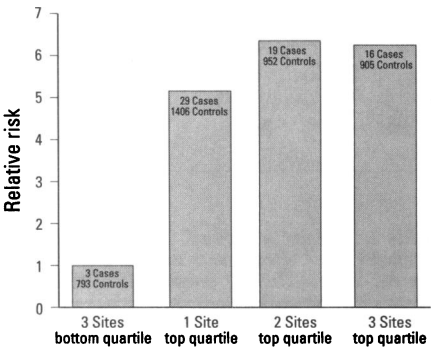

Figure 1. Relative risk of breast cancer by bone mineral density. Women with top quartile BMD at one, two, or three sites compared to women with lowest BMD at three sites.

test the hypothesis that: *a*) women with low BMD are estrogen deficient and more likely to have been placed on HRT in the past, resulting in a substantial selection bias for HRT and risk of breast cancer (i.e. low risk women with low BMD were placed on HRT), and *b*) the reported weak or lack of association between HRT and breast cancer would be due to the selection of women with low BMD and lower risk of breast cancer.

We created an artificial sample of 40,000 women, assuming that 30% would be hormone (estrogen or estrogen/progesterone) users, and that among the hormone users, 50% would be in the lowest quartile of BMD, 25% in quartile two, 15% in quartile three, and 10% in quartile four (Table 1). We believe that this was reasonable, as women with artificial menopause, symptomatology, or risk of osteoporosis were more likely to have been placed on HRT in the past.

We used the incidence rates from the SOF (*41*), approximately 4.5/1000/year. We estimated that over 4 years there would be approximately 72 cases of incident breast cancer. The rates would vary from 2.5/1000 in the lowest quartile of BMD to 5.5/1000/year in the highest quartile (Table 1). We then presumed that the risk of breast cancer was increased 3-fold among hormone users. An estimated 2.3-fold risk would be observed without knowledge of selection for BMD comparing HRT users and nonusers. A true 2-fold increased risk, again without knowledge of selection for BMD, would appear to be a 1.3-fold increased risk, and true 1.5-fold increased risk due to HRT would appear to be a 1.1-fold increase in the risk of breast cancer. It is possible, therefore, that the relatively low risk of breast cancer among HRT users reported in some past studies, was due to selection for women who had lower endogenous estrogen levels, i.e., lower BMD, initially at lower risk of breast cancer.

We next selected HRT so that its major indications were the primary prevention of cardiovascular disease (i.e., high LDLc, low high-density lipoprotein cholesterol [HDLc], obesity) and osteoporosis. Women were placed on HRT without knowledge of their BMD. It is much more likely now that women with higher BMD and, perhaps, greater risk of breast cancer would be placed on HRT. We therefore modeled the use of HRT presuming there was no selection for BMD and evaluated the potential risk of breast cancer associated with BMD and HRT.

Women with high BMD (top quartile) would have an estimated 3.3-fold increased risk of breast cancer with a 1.5-fold increase due to HRT, as compared to women with low BMD not on HRT (Table 2). Over a 20-year period, between the ages of 52 to 72 years, these women would have an estimated 17% risk of breast cancer (one in six). This is substantially higher than their risk of myocardial infarction. For example, in the Framingham Study follow-up, the cumulative incidence of coronary heart disease (excluding angina pectoris), in women age 50 to 70 was about 11%, similar to the incidence of breast cancer for women in quartile four of BMD, even without added HRT.

The model presumes a relatively simple additive effect of BMD and use of HRT. It is possible that the use of HRT only increases the risk of breast cancer among women with low BMD and estrogen deficiency relative to that of all other women, and would have little effect on women who already had high BMD. If this model were true, women with low BMD, even with a 3-fold increased risk of breast cancer, would not be identified in current epidemiological studies; the overall risk associated with HRT compared with non-HRT for the entire population would only be a 1.4-fold increased risk, similar to that found in many of the current studies, unless measures of BMD were available.

The increased risk of breast cancer may be greater in women with high BMD and more than additive. If such a situation exists, it is possible that there may be a group of women at extremely high risk of breast cancer who might inadvertently be placed on HRT for cardiovascular protection and be at extremely high risk of breast cancer.

Table 1. Observed annual risk of breast cancer by quartile of bone density and use of HRT among a cohort of 40,000 women. Assumes a 3-fold increased risk of breast cancer among HRT users, and that women with low bone density are more likely to use HRT.

Incidence/ 1000 quartile		Not on HRT			On HRT		
		n	Breast cancer, no. cases	RR	*n*	HRT, %	3-fold increased risk, no. cases
I	2.5	4,000	10	3	6,000	50	45
II	4.0	7,000	28	3	3,000	25	36
III	5.0	8,200	41	3	1,800	15	27
IV	5.5	8,800	48	3	1,200	10	19
Total		28,000	127		12,000	100	127
Rate			4.5	2.3			10.6

Table 2. Estimated relative risk of breast cancer for women in the highest quartile of BMD assuming a 2.2-fold increased risk of breast cancer between highest and lowest quartile of BMD, and varying risk due to HRT (incidence quartile 1= 2.5/1000, quartile 4 = 5.5/1000/year).

Breast cancer risk due to HRT	Estimated incidence, quartile 4	Risk compared to quartile 1 No HRT, 2.5/1000	Cumulative incidence 20-year breast cancer, %
3	16.5	6.6	33.0
2	11.0	4.4	22.0
1.5	8.3	3.3	16.6
1.0	5.5	2.2	11.0

Discussion

Why exogenous estrogens or estrogen/progesterone, i.e., in HRT, are not associated with a substantial increased risk of breast cancer among postmenopausal women, given that endogenous estrogens are an important determinant of breast cancer, is a major unanswered question. Possible explanations for the failure to document an increased risk of breast cancer among HRT users has focused on several areas: *a*) The duration of follow-up from time of initial HRT use and its association in several studies with an increased risk of breast cancer. The discovery in 1975 of the association between estrogen therapy and uterine cancer resulted in substantial reduction in the use of estrogen, especially among women with intact uteruses. It was not until approximately 1987 (*45*) that HRT began to substantially increase again, primarily because of the availability of estrogen/progesterone combinations that reduced the risk of uterine cancer, and growing evidence for the possible benefits of estrogen replacement therapy in reducing the risks of osteoporotic fracture and coronary heart disease. Thus, the majority of current hormone users have been on HRT for a relatively short length of time (perhaps

from the late 1980s to the 1990s), or are women who had an artificial menopause or hysterectomy and therefore did not have the risk of uterine cancer. Another major problem is selection for longer term use. Many older women do not continue hormone therapy (*46*). In the Perimenopausal Estrogen/Progesterone Intervention (PEPI) trial, 37% of the women with intact uteruses on conjugated estrogens alone discontinued therapy by 36 months (*47*). This was explained by the high rates of adenomatous or atypical endometrial hyperplasia in women assigned to unopposed estrogens. The incidence of women who were unable to continue unopposed estrogens for any reason was 20% within 1 year, 45% at 2 years, and 55% at 3 years. It is possible, based on these results from PEPI, that women with intact uteruses who have been on long-term estrogen therapy in the past have metabolized the drug differently. Women with a lower estrogen exposure at the uterus and perhaps also at the breast would have a differential tissue response to estrogens including absence of hyperplasia, bleeding, and perhaps breast neoplasia.

Other studies have also shown a fairly high frequency of bleeding associated with both estrogens alone, as well as estrogens and progesterone, among postmenopausal hormone users (*48*), and clearly there is a selection for women who will stay on long-term therapy. *b*) HRT depresses serum levels of insulin-like growth factor I (IGF-1), while endogenous estrogens stimulate IGF-1 levels. Premenopausal women have higher IGF-1 levels than postmenopausal women. IGF-1 or IGF-2 and their binding proteins may be important for growth of breast cancer cells (*49*). However, the autocrine/paracrine levels of IGF-1 or -2 at the breast, may have little relationship to blood levels (*50*). *c*)The most likely hypothesis to explain why HRT is not associated with a greater risk of breast cancer is related to selection for HRT use, including prior artificial menopause or hysterectomy, low body weight, and greater prevalence of menopausal symptomatology, all of which are associated with low blood estrogen levels.

Several studies have attempted to adjust for potential selection bias, HRT use, and risk of breast cancer. The adjustment factors may have little association with risk of postmenopausal breast cancer, especially among older women. The adjustment variables may not be good measures of prior endogenous estrogen exposure, especially with the biological dose at the breast and other tissues.

In recent years, the current use of HRT for the prevention of cardiovascular disease and osteoporosis, as well as a shorter term use for the treatment of menopausal symptomatology and estrogen deficiency has greatly increased the population of women on HRT. Women now remain on HRT for longer periods of time and start therapy soon after the menopause, in order to reduce the risks of both coronary heart disease and osteoporosis.

The combination of long-term use and therapy initiation fairly early after the menopause will ultimately result in many more long-term estrogen or estrogen/progesterone users. Furthermore, whereas women were selected for HRT in the past based on relative estrogen deficiency, many of the current potential long-term users are being placed on therapy for prophylaxis, especially for coronary heart disease and osteoporosis. This presents an interesting problem, because obese women are more likely to have lower HDLc and higher LDLc after the menopause and, therefore, would be considered to be candidates for hormone replacement therapy (*51*). However, such women probably have higher estrogen levels, especially if they gained weight from the pre- to the postmenopause, resulting in an increase in their LDLc, decrease in their HDLc, and possibly an increase in their risk of breast cancer. It is possible that women at greater risk of breast cancer because of long-term higher levels of endogenous estrogens, are now being exposed to further high levels of estrogens with estrogen/progesterone therapy.

The increased risk of breast cancer in older women associated with higher BMD and presumably increased endogenous estrogen exposure may not result in metastatic disease or substantial morbidity or mortality. It is possible that without further exposure to other carcinogens or a genetic susceptibility to metastatic disease, the breast cancers identified primarily by mammography among older women are of little clinical importance.

There could be an important interaction between stimulants of breast glandular epithelial cells by estrogen and exposure to carcinogens. The progression to metastatic disease may be linked to either further exposure to carcinogens or genetic host susceptibility, including metabolism of estrogen such as through 2- and 16α-hydroxylation of estrone (*9*).

Current clinical trials, including the Women's Health Initiative (i.e., very low fat/high fiber intake) (*52*), the tamoxifen trial (the primary prevention of breast cancer in high risk women) (*53*) and trials of luteinizing hormone-releasing hormone antagonists among women at very high risk of premenopausal breast cancer (*54*), have the potential for substantially modifying the risk, primary prevention, and decreased incidence of breast cancer. The difficulties in maintaining long-term weight reduction, especially among postmenopausal women, have precluded very important trials of the effects of weight loss among postmenopausal women and the risks of breast cancer.

Potential risks are associated with the reduction of endogenous estrogen levels across the population, since BMD is directly related to endogenous estrogen levels. Reduction of estrogen levels may result in decreased BMD and an increase in risk of osteoporotic fractures. Similarly, high endogenous estrogen levels among postmenopausal women may provide protection against cardiovascular disease and reduction of these levels could be associated with an increase in coronary heart disease.

It has taken at least 15 years to recognize the association between estrogen therapy and uterine cancer. The use of HRT continues to increase in the United States. The indications for therapy are changing towards a view of menopause as a disease, and the indication for hormone therapy towards a modifier of the potential risk of cardiovascular disease and osteoporosis.

In the future, the incidence of morbidity and mortality due to breast cancer for women on estrogen or estrogen/progesterone therapy for longer periods of time may increase. The absence of good clinical trials, to evaluate both the benefits in terms of osteoporosis and cardiovascular disease, and the risks of breast cancer among women on HRT, is extremely unfortunate.

The most likely scenario is that HRT is of benefit for some women at high risk for osteoporosis and coronary heart disease, and not beneficial for women at higher risk for breast cancer. The availability of alternative therapies for both coronary heart disease and osteoporosis further increases the need to determine, in clinical trials, the risks and benefits of hormone replacement therapy. It is now feasible to quantify a woman's risk of cardiovascular disease, osteoporosis, and likely breast cancer. Therapies can be tailored for the individual needs of a woman based on risk evaluation rather than the classification of menopause as a disease requiring universal hormone replacement therapy.

REFERENCES

1. Barrett-Connor E. Hormone replacement and cancer. Br Med Bull 48:345–355 (1992).
2. Cauley JA, Cummings SR, Dennis DM, Mascioli SR, Seeley DG. Prevalence and determinants of estrogen replacement therapy in elderly women. Am J Obstet Gynecol 163(5):1438–1444 (1990).
3. Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy—long-term follow-up of a Swedish cohort. Int J Cancer 67:327-332 (1996).
4. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernster VL, Cummings SR. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 117:1016–1037 (1992).
5. Kuller LH. The etiology of breast cancer—from epidemiology to prevention. Public Health Rev 23:157–213 (1995).
6 Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev 4:567–571 (1995).
7. Land CE, Hayakawa N, Machado SG, Yamada Y, Pike MC, Akiba S, Tokunaga M. A case-control interview study of breast cancer among Japanese A-bomb survivors. II: Interactions with radiation dose. Cancer Causes Control 5:167–176 (1994).
8. Adlercreutz H. Western diet and Western diseases: some hormonal and biochemical mechanisms and associations. Scand J Clin Lab Invest 50(S201):3–23 (1990).
9. Bradlow HL, Hershcopf RJ, Fishman J. Oestradiol 16α-hydroxylase: a risk marker for breast cancer. Cancer Surv 5:573–583 (1986).
10. Rebbeck TR, Rosvold EA, Duggan DJ, Zhang J, Buetow KH. Genetics of CYP1A1: coamplification of specific alleles by polymerase chain reaction and association with breast cancer. Cancer Epidemiol Biomarkers Prev 3:511–514 (1994).
11. Trachman TE, Chen X, Toniolo P, Garte SJ. A CYP1A1 restriction fragment length polymorphism is associated with breast cancer in African-American women. Cancer Res 55:3757–3758 (1995).
12. Leygue ER, Watson PH, Murphy LC. Estrogen receptor variants in normal human mammary tissue. J Natl Cancer Inst 88:284–290 (1996).
13. Ford D, Easton F, Peto J. Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 57:1457–1462 (1995).
14. Pike MC, Spicer DV, Dalmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 15:17–35 (1993).
15. Jaffe RB. The menopause and perimenopausal period. Reproductive endocrinology: physiology, pathophysiology and clinical management. Philadelphia:W.B. Sanders, 1986.
16. Carr BR. Disorders of the Ovary and Female Reproductive Tract. In: Williams Textbook of Endocrinology. 8th ed. Philadelphia:W.B. Saunders, 1992;733–798.
17. Gow SM, Turner EI, Glasier A. The clinical biochemistry of the menopause and hormone replacement therapy. Ann Clin Biochem 31:509–528 (1994).
18. Brinton LA, Schairer C, Hoover RN, Fraumeni JF Jr. Menstrual factors and risk of breast cancer. Cancer Invest 6:245–254 (1988).
19. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. One hundred thirty-three randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 339:1–15, 71–85 (1992).
20. Nayfield SG, Karp JE, Ford LG, Dorr FP, Kramer BS. Potential role of tamoxifen in prevention of breast cancer. J Natl Cancer Inst 83:1450–1459 (1991).
21. Vermeulen A. Adrenal function in postmenopausal women. In: The menopause: clinical endocrinological and pathophysiological aspects (Fioretti P, Martini L, Melis GB, Yen SSC, eds). New York:Academic Press, 1992;133–138.
22. Judd H, Judd GE, Lucas WE, Yen SC. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 39:1020 (1974).
23. Cauley JA, Gutai JP, Kuller LH, Powell JP. Reliability and interrelations among serum sex hormones in postmenopausal women. Am J Epidemiol 133:50–57 (1991).
24. Kuller LH, Gutai JP, Meilahn E, Matthews KA, Plantinga P. Relationship of endogenous sex steroid hormones to lipids and apoproteins in postmenopausal women. Arteriosclerosis 10:1058–1066 (1990).
25. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, Longcope L, Speizer FE. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 87:1297–1302 (1995).
26. Matthews KA, Wing RR, Kuller LH, Meilahn EN, Plantinga P. Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. Arch Intern Med 154:2349–2355 (1994).
27. Cauley JA, Gutai JP, Kuller LH, Scott J, Mevitt MC. Black-white differences in serum sex hormones and bone mineral density. Am J Epidemiol 139:1035–1046 (1994).
28. Meilahn E, Herzog H, Sutton-Tyrrell K, Gutai J, Kuller L, Matthews K. Endogenous estrogen levels, lipoproteins and carotid artery wall thickness among postmenopausal women. Circulation 93:10 (1996).
29. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, Strax P, Pasternack BS. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 87:190–197 (1995).
30. Petrakis NL. Nipple aspirate fluid in epidemiologic studies of breast disease. Epidemiol Rev 15:188–195 (1993).
31. Santen RJ, Leszczynski, Tilson-Mallet N, Feil PO, Wright C, Manni A, Santner SJ. Enzymatic control of estrogen production in human breast cancer: relative significance of aromatase versus sulfatase pathways. Ann NY Acad Sci 464:126–137 (1986).
32. Azziz R. Reproductive endocrinologic alterations in female asymptomatic obesity. Fertil Steril 52:703–725 (1989).
33. Morabia A, Wynder EL. Epidemiology and natural history of breast cancer: implications for the body weight-breast cancer controversy. Surg Clin North Am 70:739–752 (1990).
34. Schapira DV, Clard RA, Wolff PA, Jarrett AR, Kumar NB, Aziz NM. Visceral obesity and breast cancer risk. Cancer 74:632–639 (1994).
35. Dorgan JF, Longcope C, Stephenson HE Jr, Falk RT, Miller R, Franz C, Kahle L, Campbell WS, Tangrea JA, Schatzkin A. Relation of prediagnostic serum estrogen and androgen levels to breast cancer risk. Cancer Epidemiol Biomarkers Prev 5:533–539 (1996).
36. Persson I, Adami HO, McLaughlin JK, Naessen T, Fraumeni JF. Reduced risk of breast and endometrial cancer among women with hip fractures (Sweden). Cancer Causes Control 5:523–528 (1994).
37. Eriksen EF, Colvard DS, Berg NJ, Graham ML, Mann KG, Spelsburg TC, Riggs BL. Evidence of estrogen receptors in normal human osteoblast-like cells. Science 241:84–86 (1988).
38. Fox KM, Magaziner J, Sherwin R, Scott JC, Plato CC, Nevitt A, Cummings S. Reproductive correlates of bone mass in elderly women. J Bone Min Res 8:901–908 (1993).
39. Nilas L, Christiansen C. Bone mass and its relationship to age and the menopause. J Clin Endocrinol Metab 65:697–702 (1987).
40. Lindsay R. Hormone replacement therapy for prevention and treatment of osteoporosis. Am J Med 95:375–395 (1993).
41. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and the risk of breast

cancer in older women. The Study of Osteoporotic Fractures. JAMA 276:1404–1408 (1996).
42. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley JA, Genant HK, Mascioli SR, Scott JC, Seeley DG, Steiger P, Vogt TM and the Study of Osteoporotic Research Group. Appendicular bone density and age predict hip fracture in women. JAMA 263:665–668 (1990).
43. Miller BA, Ries LAG, Hankey BF, Kosary CL, Harras A, Devesa SS, Edwards BK, eds. SEER Cancer Statistics Review, 1973–1990, National Cancer Institute. NIH Publ No. 93-2789, 1993.
44. Cummings SR, Cauley JA, Lucas FL, Browner WS, Kuller LH. [Abstract] Women with vertebral fractures have a very low risk of breast cancer unless they take estrogen. The Study of Osteoporotic Fractures. ASBMR 18th Annual Meeting; J Bone Min Res 11:S139 (1996).
45. Wysowski DK, Golden L, Burke L. Use of menopausal estrogens and medroxyprogesterone in the United States, 1982–1992. Obstet Gynecol 85:6–10 (1995).
46. Jonas HA, Kronmal RA, Psaty BM, Manolio TA, Meilahn EH, Tell GS, Tracy RP, Robbins JA, Anton-Culver H for the Cardiovascular Health Study Collaborative Research Group. Current estrogen-progestin and estrogen replacement therapy in elderly women: association with carotid atherosclerosis. Ann Epidemiol 6:314–323 (1996).
47. Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 275:370–375 (1996).
48. Archer DF, Pickar JH, Bottiglioni F for the Menopause Study Group. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. Obstet Gynecol 83:686–692 (1994).
49. Railo MJ, Smitten KV, Pekonen F. The prognostic value of insulin-like growth factor-I in breast cancer patients. Results of a follow-up study on 126 patients. Eur J Cancer 30A:307–311 (1994).
50. Schmid C. IGF's: function and clinical importance. The regulation of osteoblast function by hormones and cytokines with special reference to insulin-like growth factors and their binding proteins. J Int Med 234:535–542 (1993).
51. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga P. Weight gain at the time of the menopause. Arch Intern Med 151:97–102 (1991).
52. Rossouw JE, Finnegan CP, Harlow WR, Pinn VW, Clifford C, McGowan JA. The evolution of the Women's Health Initiative: Perspectives from the NIH. J Am Med Women's Assoc 50:50–55 (1994).
53. Jordan VC. A current view of tamoxifen for the treatment and prevention of breast cancer. Fourteenth Gaddum memorial lecture. Br J Pharmacol 110:507–517 (1993).
54. Spicer DV, Pike MC. Sex steroids and breast cancer prevention. Monogr Natl Cancer Inst 16:139–147 (1994).